

Hereditary Colorectal Cancer: An Updated Review

Part II: The Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer)

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Abstract: Hereditary nonpolyposis colorectal cancer, also known as the Lynch syndrome, is the most common of the hereditary disorders associated with colorectal cancer. Because the Lynch syndrome lacks definitive premorbid phenotypic features, diagnosis depends on a well-documented family history and knowledge of the natural history of the condition. This review, which follows an earlier review of hereditary polyposis syndromes (*Gastroenterology & Hepatology*, 2005;1:39-48) discusses the history, clinical features, diagnosis, and management of Lynch syndrome. Patient outcomes, medicolegal issues, and future research directions are also discussed.

Hereditary nonpolyposis colorectal cancer (HNPCC, also known as the Lynch syndrome) is the most common hereditary disorder predisposing to colorectal cancer (CRC).^{1,2} It is an autosomal dominant disorder wherein a germline mutation in 1 of the mismatch repair (MMR) genes (most often *MSH2* or *MLH1*) can be demonstrated in approximately 40–60% of the families meeting its clinical criteria. Its incidence remains elusive and accounts for approximately 2% of the CRC burden in the United States,³ although higher estimates have been given.^{1,2}

History of the Lynch Syndrome

The history of the Lynch syndrome dates to an observation of a familial cluster of cancer by Aldred Warthin, then a pathologist at the University of Michigan School of Medicine.⁴ Specifically, Dr. Warthin became deeply moved when his seamstress, in 1895, told him that she would likely die of cancer of the colon, stomach, or female organs because of the enormous proclivity for these cancers in her family. Warthin listened to her intently, developed her pedigree, along with those of similar cancer-prone families, and published this work in 1913.⁵ (Just as she had told Warthin, the seamstress died at a young age of metastatic endometrial carcinoma.) He updated his study of the seamstress's family in 1925.⁶ The family has since been known as Family G.

In 1966, Lynch and colleagues⁷ subsequently described the natural history and genetics of familial aggregations of cancer in 2 large Midwestern kindreds (Families N and M). Dr. A. James French, Warthin's successor as chairman of pathology at the University of Michigan School of Medicine, heard about Lynch's research on Fam-

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ilies N and M and recalled that Warthin had discovered a similar family (Family G) in 1895. He invited Lynch to take custody of the detailed documents and pathology specimens that the meticulous Warthin had investigated, catalogued, and published over a span of more than 30 years. An update on Family G was subsequently published in 1971,⁸ and is discussed in a more detailed review of the history of HNPCC.⁹ Through the use of conversion technology, an *MSH2* mutation was identified in Family G in the year 2000.¹⁰

Mismatch Repair Mutations and the Lynch Syndrome

The molecular genetic era dealing with HNPCC began when Peltomäki and coworkers¹¹ identified a susceptibility locus on chromosome 2p through linkage analysis as a site for a gene predisposing to HNPCC. Shortly thereafter, a second susceptibility locus on chromosome 3p believed to be etiologic for HNPCC was identified by Lindblom and associates in Sweden.¹² At the 2p and 3p loci, HNPCC genes were subsequently identified, namely *MSH2* and *MLH1*. These genes encode proteins involved in the identification and repair of DNA mismatch errors.¹³⁻¹⁶ More than 400 different pathogenic mutations have been registered in the International Database of Mutations in HNPCC Kindreds (available at <http://www.nfdht.nl>).

Mutations in 6 different MMR genes have been identified in HNPCC patients^{17,18}: *MLH1*,¹⁵ located on chromosome 3p21.3; *MSH2*,^{13,14} and *MSH6*,¹⁹ both located on 2p21; *PMS2*,²⁰ located on 7p22; *MLH3*,^{21,22} located on 14q24.3; and *PMS1*,²⁰ located on 2q31-q33. However, only 40–60% of HNPCC patients harbor identifiable germline mutations, most commonly *MSH2* and *MLH1* mutations.²³ Specifically, approximately 90% of the identified HNPCC mutations involve *MLH1* or *MSH2*, and mutations in the *MSH6* gene account for approximately 10%. *MSH6* mutations appear to predispose to an atypical form of HNPCC characterized by an excess of endometrial cancer and a deficit of CRC.²⁴ These findings suggest that other genes, including modifier genes, may be of etiologic importance in HNPCC; differing mutation types, environmental factors, and/or chance could also explain the etiology of HNPCC in which no known cancer-causative germline mutations have been identified.^{2,18}

DNA Mismatch Repair and Immunohistochemistry in the Lynch Syndrome

All cells of Lynch syndrome-affected individuals carry a nonfunctioning allele of a DNA MMR gene; if the wild-type allele is lost or inactivated, the cell can no longer repair the DNA mismatches that inevitably arise dur-

ing DNA replication. Cells with defective DNA MMR genes accumulate mutations at a very high rate (as much as 1,000 times that of normal cells). Because DNA mismatches are more likely to occur in DNA microsatellites (areas with multiple repeats of 1 nucleotide or 1 pair of nucleotides), defective DNA MMR leads to the phenomenon of microsatellite instability (MSI), in which the progeny of the defective cells have varying lengths of a given microsatellite.

The predilection of DNA mismatches for mono- and dinucleotide repeats plays a deciding role in the genetic mutations contributing to carcinogenesis. Nearly all colon cancers with MSI have mutations in the transforming growth factor β (TGF β) type II receptor (TGFB2R) and BAX genes, and those mutations are located in repeating sequences. Mutation of TGFB2R leads to escape from the growth-inhibitory effects of TGF β , whereas mutation of BAX interferes with its proapoptotic effect. Thus, carcinogenesis in colon cancers with MSI may involve mutations in critical genes different from those involved in other colon cancers (eg, APC, K-RAS, p53).

In the hereditary setting, one allele carries a germline mutation; when the second allele is lost or inactivated, it is possible that the mutant allele will produce a truncated or otherwise altered protein that stains normally but functions abnormally, thus resulting in a falsely normal immunohistochemical stain. Lindor and colleagues²⁵ found that 27 of 818 tumors with intact staining of *MLH1* and *MSH2* were MSI-high (MSI-H). The authors concluded that immunohistochemistry (IHC) is a specific (100%) and sensitive (92.3%) screening tool, but that some MSI-H tumors will be missed if only IHC is performed.

Clinical Features

Unlike the several hereditary adenomatous and hamartomatous colonic polyposis syndromes, the Lynch syndrome lacks striking premorbid phenotypic features which, when identified, could lead to a hereditary cancer syndrome diagnosis. Therefore, the clinician must rely heavily upon a well-documented family history, coupled with full knowledge of the natural history of HNPCC and the spectrum of extracolonic cancers that are integral to the syndrome (particularly carcinoma of the endometrium; also cancers of the ovaries, stomach, small bowel, hepatobiliary tract, and upper uroepithelial tract, brain tumors, and the cutaneous features of the Muir-Torre syndrome [MTS], discussed below).^{1,2}

Prostate Cancer in Lynch Syndrome

Soravia and colleagues²⁶ suggest that prostate cancer may be an integral lesion in the Lynch syndrome. They report a family wherein the proband had 3 metachronous

adenocarcinomas of the colon and rectum, at ages 54, 57, and 60, and presented with an adenocarcinoma of the prostate at age 61. These investigators performed IHC staining of colonic, rectal, and prostatic tumor tissues and therein found a lack of expression of *MSH2* and *MSH6*. MSI was evidenced in the rectal, colonic, and prostatic tumors. Since the family fit the Amsterdam criteria for the Lynch syndrome (Table 1), molecular genetic studies were initiated following the proband's son's manifestation of CRC at age 35. The authors reported that Southern blot analysis led to identification of a novel genomic deletion encompassing exon 5 of the *MSH2* gene; to the best of their knowledge, this is the first report wherein MSI and IHC analysis of a prostate adenocarcinoma clearly linked it to a germline MMR mutation. The authors, therefore, appropriately suggest that prostate cancer be included in the Lynch syndrome tumor spectrum, also noting that there have been occasional reports in the literature^{27,28} of prostate carcinoma in Lynch syndrome kindreds.

Rare Lynch Syndrome Tumors

The molecular pathogenesis of tumors outside the usual tumor spectrum of the Lynch syndrome remains elusive. It is unclear if these tumors are related to defects in DNA MMR or whether they have arisen independently of MMR defect.²⁹

Broaddus and associates²⁹ described 2 young *MSH2* mutation carriers with tumors not usually associated with the Lynch syndrome: one, aged 34, developed an adrenal cortical carcinoma and the second, a 39-year-old woman, had a diagnosis of anaplastic carcinoma of the thyroid. Both of these patients were members of families that fulfilled Amsterdam criteria for HNPCC (Table 1). The adrenal and thyroid tumors both showed a complete loss of immunohistochemical expression for the *MSH2* protein. Furthermore, neither of these tumors was found to be MSI-H based upon MSI analysis using the National Cancer Institute panel of 5 microsatellite markers.

Sijmons and coworkers³⁰ reported a malignant fibrous histiocytoma arising in a patient with a germline *MSH2* mutation and a positive family history for the Lynch syndrome.

A man with a germline *MLH1* mutation and a positive family history developed infiltrating ductal carcinoma of the breast 30 years after early-onset CRC. The breast tumor had MSI positivity (marked by BAT-26 and BAT-40). The wild-type *MLH1* allele was lost in the breast tumor tissue compared to normal tissue and was related to the underlying germline mutation of *MLH1*.³¹

Berends et al³² reported a woman with an *MSH2* germline mutation, ovarian cancer, and 3 metachronous CRCs; she was also found to have an adrenal cortical

Table 1. Amsterdam I and Amsterdam II Criteria and Bethesda Guidelines

Amsterdam I Criteria for Diagnosing the Lynch Syndrome ¹⁰³
<ul style="list-style-type: none"> • At least 3 relatives with histologically verified colorectal cancer: <ul style="list-style-type: none"> - One is a first-degree relative of the others - At least 2 successive generations affected - At least 1 of the relatives with colorectal cancer diagnosed at <50 years of age - Familial adenomatous polyposis has been excluded
Amsterdam II Criteria for Diagnosing the Lynch Syndrome ¹⁰⁴
<ul style="list-style-type: none"> • At least 3 relatives with HNPCC-associated cancer.* <ul style="list-style-type: none"> - One is a first-degree relative of the others - At least 2 successive generations affected - At least 1 of the HNPCC-associated cancers should be diagnosed at <50 years of age - Familial adenomatous polyposis should be excluded in any colorectal cancer cases; tumors should be verified whenever possible
Bethesda Guidelines for Testing of Colorectal Tumors for Microsatellite Instability ¹⁰⁵
<ul style="list-style-type: none"> - Colorectal cancer diagnosed in a patient who is <50 years of age - Presence of synchronous or metachronous colorectal, or other HNPCC-associated tumors,* regardless of age - Colorectal cancer with the MSI-H[†] histology[‡] diagnosed in a patient who is <60 years of age[§] - Colorectal cancer or HNPCC-associated tumor diagnosed under age 50 years in at least 1 first-degree relative - Colorectal cancer or HNPCC-associated tumor diagnosed at any age in 2 first- or second-degree relatives

*Hereditary nonpolyposis colorectal cancer (HNPCC)-associated tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter or renal pelvis, biliary tract, and brain (usually glioblastoma, as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

† Microsatellite instability–high (MSI-H) in tumors refers to changes in 2 or more of the 5 National Cancer Institute–recommended panels of microsatellite markers.

‡ Presence of tumor-infiltrating lymphocytes, Crohn's disease–like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

§ There was no consensus among the Workshop participants on whether to include the age criteria; participants voted to keep “<60 years of age” in the guidelines.

|| These criteria have been reworded to clarify the Revised Bethesda Guidelines.

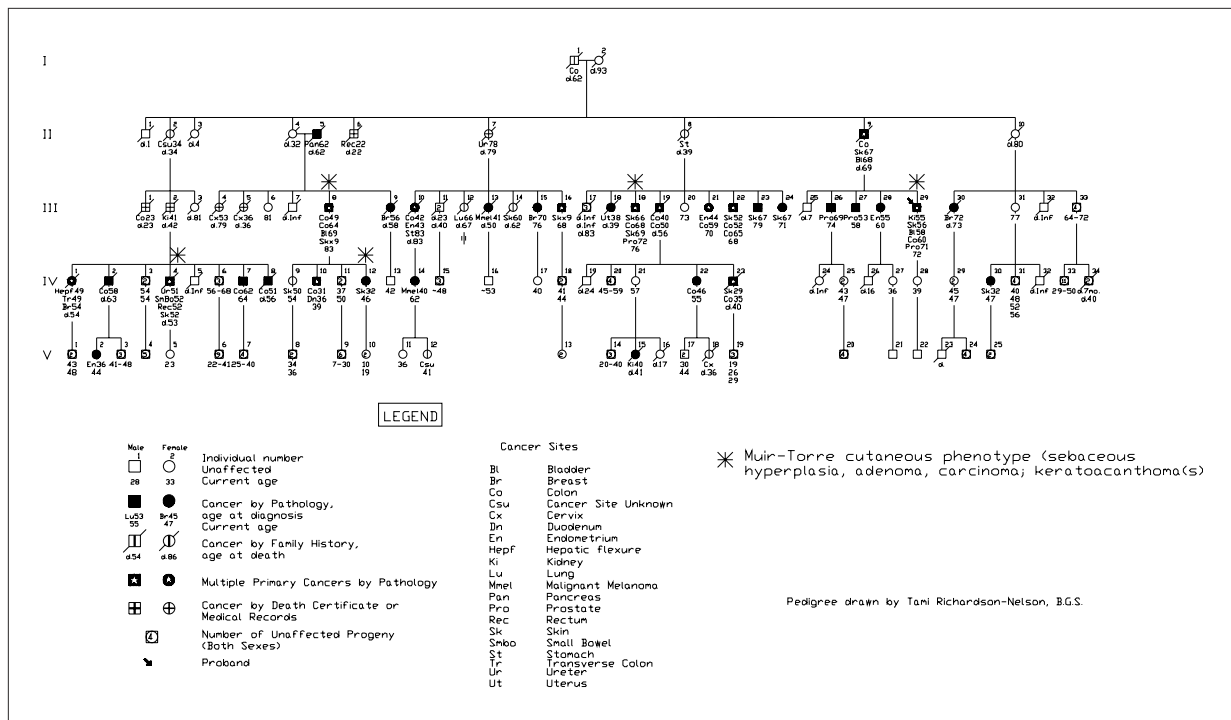


Figure 1. Pedigree of a Muir-Torre syndrome family with involvement of multiple primary cancers.

Reprinted from Lynch et al. *Am J Gastroenterol.* 2003;98:664-670.

carcinoma. It is of interest that the proband in Family N7 manifested adrenal cortical carcinoma.

We have recently been consulted regarding a patient with the *MSH2* del 1-6 mutation and the exceedingly rare proliferative trichilemmoma tumor.

Muir-Torre Syndrome

Muir-Torre syndrome is the only form of the Lynch syndrome to manifest premorbid phenotypic features. Since 1981, when Lynch and colleagues³³ reported the first examples of MTS in Lynch syndrome families, several papers³⁴⁻³⁷ have elucidated in greater detail the clinical and molecular genetic features of MTS. They suggest that the identification of MTS cutaneous features, namely sebaceous adenomas, carcinomas, and multiple keratoacanthomas, in association with the types of visceral cancer found in the Lynch syndrome, merit a detailed family history in search of evidence of the Lynch syndrome. Finally, patients with these cutaneous stigmata merit DNA germline testing, particularly for evidence of the *MSH2* germline mutation, which appears to be more frequent in MTS than is its *MLH1* mutation counterpart. Figure 1 shows the pedigree of an MTS syndrome family with an identified *MSH2* mutation.

Diagnosis and Management

An algorithm that encompasses the diagnosis and management of the Lynch syndrome is shown in Part A of Figure 2. Part B of this figure shows components that collectively will provide useful diagnostic clues to the natural history of the Lynch syndrome. In Table 1, the Amsterdam I and II criteria for diagnosing Lynch syndrome and the Bethesda guidelines for testing colorectal tumors for MSI are shown.

Family pedigree should provide the basis for the identification of candidates for screening, management, and germline testing. First-degree relatives of cancer syndrome affecteds or bearers of one of the cancer-causing germline mutations (*MSH2*, *MLH1*, *MSH6*) would therefore become candidates for intensive lifelong surveillance and management should they share the deleterious germline mutation.

However, it is necessary to consider that upward of 40% of otherwise classical Lynch syndrome kindreds may not harbor any known germline mutation. This suggests that other mutations yet to be identified may be causal and/or reduced penetrance of a known mutation may obfuscate the ability to discern an individual's cancer risk status.

Survival Advantage

Popat and colleagues⁵⁷ evaluated studies that stratified survival among CRC patients by MSI status. Those with MSI were found to have a significantly better prognosis when compared to patients with intact MMR. However, a benefit of adjuvant chemotherapy in locally advanced CRC with MSI will require additional investigation. MSI-positive CRCs are more often proximal, poorly differentiated, and mucinous, and they manifest marked leukocyte infiltration and tend to retain the native diploid state. This is in comparison to chromosomally unstable tumors, which tend to be aneuploid and have no anatomic site of predilection.⁵⁷ Lynch syndrome CRCs show upward of 95% MSI positivity.⁵⁸

Multiple observational studies have shown a survival advantage for HNPCC patients when compared to sporadic colon cancer patients.⁵⁴ Gryfe and associates⁵⁵ demonstrated that HNPCC patients have improved 5-year survival (76% vs 54%) on a stage-for-stage basis compared to patients with sporadic tumors. Similarly, the overall 10-year survival rates in affected family members is better than that seen in sporadic CRC (68% vs 48%).⁵⁹

Founder Mutations

The evolution of the concept of founder mutations in noncancer disorders such as cystic fibrosis and, more recently, the Lynch syndrome, has been previously summarized.⁶⁰ Founder mutations are now being described with increasing frequency.^{61,62} In certain populations considerable enrichment of these mutations has occurred, but this is not likely to be of any selective advantage; rather genetic drift, that is, the repeated effect of chance at population bottlenecks, has provided a partial explanation. Typically, populations displaying founder effects have grown rapidly.

Prime examples are the Finns ("founded" some 2,000 years ago⁶³), Icelanders (some 1,100 years ago⁶⁴), Ashkenazi Jews (600–800 years ago⁶⁵), French Canadians, and the Amish (250–400 years ago⁶⁶). Hereditary breast cancer in Ashkenazi Jews, with cancer-causing mutations in *BRCA1* (185delAG and 5382insC) and *BRCA2* (6174delT), provides an excellent molecular and clinical example of a founder effect.^{67,68}

An especially pertinent example of the impact of a founder mutation can be seen in the Finnish experience in HNPCC.⁶⁰ Because of the extremely high incidence of 2 specific disease-causing mutations in the Finnish population,⁶³ testing for the genomic deletion of exon 16 of *MLH1*—the "Finland 1" mutation—has become part of the standard HNPCC genetic testing protocol in Finland. More recently, an *MSH2* c.1452-1455delAATG mutation

has been identified as a cause of the Lynch syndrome in a southern Chinese population.⁶⁹

Guillem and coworkers⁷⁰ reviewed the literature and, coupled with their own experiences in testing for a specific founder mutation among Ashkenazi Jews, namely the *MSH2* 1906G→C (also known as A636P), they concluded that although this mutation is rare in the general population, it is present in up to 7% of Ashkenazi Jews with early-age-of-onset CRC. They estimated that this mutation may account for up to one third of the HNPCC cases in the Ashkenazi Jewish population.

Tomlinson and colleagues⁷¹ identified a novel susceptibility gene mapped to chromosome 15q14-q22 in an Ashkenazi family with dominantly inherited predisposition to colorectal adenomas and carcinomas. The authors refer to this previously undescribed susceptibility gene as CRAC1 (colorectal adenoma and carcinoma). Interestingly, there were 2 cases of pancreatic cancer in the family, which suggests that this disease could also be phenotypically attributable to mutations in the gene. Of further interest is the fact that the family fulfills the Amsterdam criteria for HNPCC but several of the patients have more colonic adenomas than expected. Genetic linkage analysis excluded germ-line mutations in *MSH2*, *MLH1*, *PSM1*, *PMS2*, and *MSH6*.

Varley and colleagues⁷² have suggested that, in the case of non-Lynch syndrome families, certain p53 alleles confer low-penetrance predisposition to the development of cancer. They found a narrow spectrum of p53 mutations in children with adrenocortical tumors; some of the mutations had been inherited and some of the families in question had other cancers. No family met criteria for Li-Fraumeni syndrome.

The American Founder Mutation

While detection of mutations is usually performed by sequencing, it was recently reported that one class of mutations—large structural rearrangements such as large deletions—are difficult to detect by that method. However, these mutations can be readily identified by Southern hybridization,⁷³ multiplex ligation-dependent probe amplification,⁷⁴ after conversion to haploidy,^{10,75} and by PCR, as reviewed by Lynch et al.⁷⁶

One large deletion, *MSH2*del1-6,⁷⁷ also referred to as the American founder mutation (AFM), is considered to be the most common MMR gene mutation responsible for the Lynch syndrome in the United States. These findings were updated based on the study of 566 family members of 9 at-risk probands.⁷⁶ Of these, 137 individuals have been tested, and 61 showed carriage of the AFM. Three families have been found genealogically to descend from a German immigrant family that arrived in the United States in the early 1700s and first settled in Pennsylvania.

Movements of branches of the family from Pennsylvania, through North Carolina, Alabama, Kentucky, Missouri, Iowa, Nebraska, Utah, Texas, and California have been tracked. Documented carriers of the mutation have been diagnosed in 14 states. Furthermore, the deletion was not found among 417 European and Australian families with HNPCC. This study is being expanded, wherein current estimates indicate that 16,000–30,000 descendants from this original cohort are at increased risk for carriage of this *MSH2*del1-6 mutation (unpublished data, HTL, 2005).

Molecular Genetic Complexities and CRC

The issue of molecular genetics in CRC is exceedingly complex. For example, Kim et al⁷⁸ investigated 20 APC-negative Korean patients with familial adenomatous polyposis (FAP) and analyzed them for *OGGI*, *MYH*, and *MTH1* germline mutations. They also tested for *OGGI* and *MYH* mutations in 19 Lynch syndrome patients, 86 patients suspected for that disease, and 246 patients with sporadic CRC. For case-control analysis of *OGGI* R154H purposes, some 625 hereditary or sporadic CRC patients and 527 normal controls were screened. R154H was found to be a rare polymorphism associated with sporadic CRC patients, although the association was of borderline significance (OR: 3.586, $P=.53$). R154H did not segregate with cancer phenotypes. After examining the possibility of recessive inheritance of R154H, Kim et al were not able to identify any complementary mutations in *OGGI*, *MYH*, or *MTH1*. They screened for mutations of K-ras, β -catenin, APC, p53, BRAF, and MSI status in samples with R154H and they found that: "Eight somatic mutations were identified in these genes and G:C to T: A transversion mutations were not dominant in samples harboring R154H. This result raises the possibility that *OGGI* R154H may function as a low/moderate-penetrance modifier for colorectal cancer development." The authors concluded that *OGGI* R154H polymorphisms could be identified in FAP patients, sporadic colorectal cancer patients, and normal controls.

Complex genetic and environmental interactions almost certainly influence phenotypic expression in hereditary syndromes. In the case of the Lynch syndrome, Watson et al⁷⁹ investigated the effect of cigarette smoking on CRC and found a statistically significant protagonist effect on CRC in patients with the *MLH1* mutation. In the Min mouse, inheritance of the Mom1 locus decreases the size and number of intestinal polyps.⁸⁰ In human populations, Moisio and colleagues⁸¹ have shown that genetic polymorphisms in carcinogen metabolism might modify phenotype in HNPCC. They found that in patients carrying germ-line mutations of *MLH1*, a particular N-acetyltransferase 1 allele was associated with younger patient age at diagnosis and tumor location in the distal colon.

Cancer Control in Lynch Syndrome

Järvinen and colleagues⁸² demonstrated the benefit of colonoscopic screening in HNPCC through a controlled clinical trial extending over 15 years. The incidence of CRC was compared in 2 cohorts of at-risk members from 22 HNPCC families. CRC developed in 8 screened subjects (6%), compared with 19 controls (16%; $P=.014$). The CRC rate was reduced by 62% in those who were screened using colonoscopy. All CRCs in the screened group were local, causing no deaths, compared with 9 deaths caused by CRC in the controls. It was concluded that CRC screening at 3-year intervals more than halves the risk of CRC, prevents CRC deaths, and decreases overall mortality by about 65% in HNPCC families. The relatively high incidence of CRC, even in the screened subjects (albeit without deaths), in our opinion, argues for shorter screening intervals, such as 1 year. For example, Vasen and colleagues⁸³ discovered 5 interval cancers in HNPCC patients within 3.5 years following a normal colonoscopy.

We advocate annual colonoscopy, based upon the pathology phenomenon of accelerated carcinogenesis in Lynch syndrome.⁴² We initiate colonoscopy at age 25 because the average age of CRC onset is earlier in Lynch syndrome (at approximately 45 years of age) than in the general population.^{1,2}

Discussion

There is a need for a multidisciplinary group of clinicians, geneticists, and genetic counselors to diagnose, educate, and support family members at risk for hereditary CRC syndromes so they can make sound decisions about surveillance and management options. This team may then be in the enviable position to recognize patients at extremely high cancer risk who, thereby, can benefit significantly through their compliance with available cancer control measures. However, certain problems may intervene, as discussed below.

The recognition of individuals/families with hereditary forms of CRC, coupled with intensive surveillance and management programs responsive to the syndromes' genetic and natural history features, can contribute substantially to cancer control.⁸² But how do we accomplish that lifesaving feat? It is imperative that it start with diagnosis. In the case of the Lynch syndrome, the most important step in achieving this goal is the compilation of a thorough family cancer history.⁸⁴⁻⁸⁶ This is the simplest and potentially most effective approach to diagnosis and, ultimately, to effective management through the use of early and frequent colon cancer surveillance with colonoscopy. The family history should focus upon cancer of all anatomic sites, age of cancer onset, and pattern of multiple primary cancers.

Pathology documentation should be made whenever possible regarding the information in the family history.

In the case of CRC, the presence of mucoid features, signet-cell histology, and poor differentiation, particularly with early age of onset, may provide an important clue to the presence of the Lynch syndrome, as already discussed.^{43,49} It is also appropriate to consider analyzing the tumor tissue from people suspected of having Lynch syndrome for MSI.⁸⁷ When a germline mutation is identified in a family, individuals at risk for the syndrome can be offered molecular genetic testing, the sine qua non for the syndrome's diagnosis, which may then provide verification of the syndrome's presence.^{88,89}

The primary care physician or the specialist may wish to refer the patient to a hereditary-cancer specialist and genetic counselor for further evaluation should there be any remaining question about the disorder's clinical or molecular genetic diagnosis and the need for targeted surveillance and management.

Once a diagnosis of a hereditary CRC disorder is established, the proband's high-risk relatives should be notified.^{87,90} This should then be followed by genetic counseling and DNA testing in those high-risk relatives who consent. In an attempt to reduce morbidity and mortality, surveillance measures may then be instituted that reflect the natural history of the disorder (Figure 1).²

Great strides have been accomplished in the understanding of the genetic basis of human disease. Perhaps the most profound impact of this knowledge has been in the area of cancer genetics⁹¹ and, as a consequence, the public health impact of hereditary cancer is likely to increase rapidly over the next several years. For example, many hereditary high-penetrant cancer-prone germline mutations have been identified, yet we remain in the dark with respect to the contribution of low-penetrant genetic variants or polymorphisms, and the manner in which these may affect the risk of sporadic cancer development, which is still largely unknown. Research at the basic science level should help to identify those presently elusive germline variants that confer an increased susceptibility to cancer through the elucidation of the myriad complex somatic genetic events that occur in the emerging cell. The clinical translation of the significance of cancer "running in families" has become a source of major contention as a result of a veritable explosion of knowledge about cancer causality at the molecular level during the past decade.⁸⁸ This new knowledge has the potential to affect every area of cancer management and treatment. For example, Ribic et al⁹² found that adjuvant chemotherapy with 5-fluorouracil improved survival among CRC patients with MSS and MSI-low tumors but had no benefit for those with MSI-H tumors.

It is important to study HNPCC-associated MMR gene mutations particularly because of emerging evidence for their genotypic and phenotypic heterogeneity. The

findings can then be translated into specific screening and management protocols. Future projections for such mutations could even contribute to the emergence of molecular-based designer drugs developed through advances in genomics, proteomics, high-throughput screening, and bioinformatics and could be effective therapeutically for these high-cancer-risk patients, and may even influence the choice of chemotherapy drugs.

Genetic Testing: Potential Insurance and Employment Barriers

The main concerns among high-risk Lynch syndrome patients with a germline cancer-causing mutation appear to be reproductive issues, potential transmission of the deleterious gene to their progeny, and discrimination by insurance companies and/or employers. In one Lynch syndrome kindred, more than half of those patients who were found to harbor the *MSH2* mutation considered the option of prophylactic subtotal colectomy. At-risk family members sought genetic risk assessment primarily for benefit to their children and, secondarily, for their own personal health concerns. The patients who were positive for the culprit *MSH2* germline mutation had many concerns about their lifetime cancer risk.

The Genetic Alliance, a coalition of advocacy groups that supports patients with genetic disease, petitioned the US House of Representatives in April 2004 to pass the Genetic Information Nondiscrimination Act (GINA), a bill that would ban discrimination in health insurance and employment on the basis of genetic tests. This bill was passed in the Senate by a unanimous vote during the 2003 session, but at the time of this writing it is pending in the House of Representatives. Rep. Louise M. Slaughter, who has campaigned since 1995 to pass legislation banning genetic discrimination, has said, "Most people do not even realize that their employers and insurers can gather genetic information about them without their knowledge and then use it to fire them or deny coverage. Although there is a patchwork of federal and state laws that provide protection for some people, federal legislation is needed to provide strong protections for every American."⁹³

The editorial that quotes Rep. Slaughter also calls attention to the Health Insurance Portability and Accountability Act (HIPAA), which outlaws the use of genetic information to discriminate against individuals in group health insurance plans. However, there is no evidence at present that people with individual policies face such genetic discrimination,⁹³ which is why the insurance industry opposes GINA as unnecessary. Nevertheless, our experience reflects that described in a *Nature Genetics* editorial,⁹³ which said, "Large numbers of people are reluctant to undergo genetic testing, even to discover information

that would help them more effectively manage their own health, because of concerns that insurance companies will use it to deny coverage. Public perception is by no means the best reason to enact federal legislation, but given the promise of genetic medicine it would be painful indeed to squander the benefits of genetic diagnostics and treatment because of such fears." Noteworthy is the fact that genetic testing is already established as an exceedingly important clinical diagnostic tool that can greatly improve health. This technology allows many more tests as they become clinically useful, but it must be fully appreciated that genetic testing, for some patients, will elucidate potentially "bad news" that is encoded in their genomes, which explains the need for genetic counseling and prohibition of genetic discrimination.

Medicolegal Issues Pertaining to Hereditary Colorectal Cancer

Prodigious advancements in knowledge about genetic risk for cancer, its natural history, available surveillance and management, DNA testing, and the accompanying need for genetic counseling harbor legal quagmires in the court system. Some decisions affect insurers. For example, one recent case was adjudicated in favor of a patient with the hereditary breast-ovarian cancer syndrome who followed the recommendations of her gynecologic oncologist and a cancer geneticist to undergo prophylactic oophorectomy. However, her insurance company failed to reimburse her for this procedure. While petition for reimbursement was denied at the district court level, the state Supreme Court rendered a favorable decision, ordering the insurance company to provide reimbursement for the procedure.⁹⁴

Standard-of-care concerns apply to physicians as well. In the *Safer* case,⁹⁵ the litigant's father had been diagnosed with FAP at age 35 and died of metastatic CRC at age 45. The surviving spouse claimed that although the surgeon discussed her husband's diagnosis, treatment, and cancer management, he failed to disclose the genetic risk for FAP, even though the hereditary nature of FAP was known. The patient's children, ages 10 and 17 at the time of his death, were not advised to seek early colon surveillance. Subsequently, the litigant, at age 36, experienced lower abdominal pain and underwent surgery and extensive chemotherapy for CRC arising from FAP. A claim of negligence was filed against the estate of the surgeon, alleging (1) that he had a duty to warn those known to be at risk of avoidable harm from a genetically transmissible condition existing in his patient, (2) that the physician's duty did extend to members of the immediate family of his patient, and (3) that he had breached these duties. The suit was won by the plaintiff in 1996. Similar cases are likely to become more common as advances in molecular genetics outstrip the ability of physicians to stay current

in a very complex field. Even with a meticulous reading of the literature, it is unlikely that physicians can maintain follow-up with their patients to apprise them of merging discoveries pertaining to their genetic syndrome diagnosis. The physician must not only obtain a sufficiently detailed family history, he or she must also be able to suggest appropriate surveillance and management for the affected family. These are strong arguments for the development of regional hereditary CRC registries.

Conclusions and Future Directions

The rapid progress in the identification of hereditary cancer syndromes and their molecular genetic etiology during the past decade suggests very strongly that research progress will yield an astounding mass of new clinically translatable data, particularly when considering the extant heterogeneity in these disorders. For example, it is likely that more high-prevalence, low-penetrance cancer-causing mutations will be found that contribute to what we now construe as "familial clustering" of cancer.⁶¹

The ability to modulate the effects of deleterious mutations through chemoprevention will continue to grow. A large body of literature exists on chemoprevention in colon cancer (reviewed by Hawk and colleagues⁹⁶), most of it pertaining to cyclooxygenase-2 (COX-2) inhibitors. As mechanisms for genotype-environment interactions are elucidated, there will be more opportunities for therapeutic intervention.

Microarray technology will make genetic testing more widely available and less expensive. The newly developed cDNA microarray analysis provides new methodology for cancer genetic research. Bennicelli and Barr,⁹⁷ for example, have studied the implications of microarray techniques with respect to the biology of sarcomas. Therein, relevant knowledge with respect to a better comprehension of sarcoma biology has been obtained through comparative genomic hybridization and microarray techniques. It was found that these powerful technologies "will facilitate the rapid acquisition of data that provide insight into the molecular genetic and biologic basis of sarcomas."

These microarray techniques should advance the ability to distinguish between hereditary forms of cancer such as colon, breast, ovarian, and endometrial in the respective hereditary cancer syndromes, and their sporadic counterparts. For example, Kurian and colleagues⁹⁸ note that this "mini-revolution is sweeping the world of science and medicine. DNA chip or microarray technology will have a more profound impact than other recent major advances, including DNA sequencing and the polymerase chain reaction."

Gene therapy will become a reality and will lead to the ability to alter cellular function or structure at the molecular level by replacing lost or defective genes

or adding genes known to produce beneficial proteins. Diseases ranging from inborn errors of metabolism to atherosclerosis to cancer should be amenable to treatment with molecular techniques. For example, phase I clinical trials show that p53 replacement therapy induces tumor regression in some lung cancer patients.⁹⁹ Patients known to carry mutations in cancer-susceptibility genes should be ideal candidates for molecular intervention.

Will molecular genetic research pave the way for CRC prevention? A prime example of this potential prevention objective relates to the fact that a significantly increased expression of COX-2, a prostaglandin-synthesizing enzyme that is pharmacologically inhibited by non-steroidal anti-inflammatory drugs such as indomethacin, sulindac, and celecoxib, is a significant early carcinogenic event in CRC. Specifically, these agents have been shown to promote colonic adenoma regression in patients with FAP.^{96,100,101}

Recently, Yan et al¹⁰² found that in addition to inducing the expression of COX-2, CRCs target “the prostaglandin biogenesis pathway by ubiquitously abrogating expression of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a prostaglandin-degrading enzyme that physiologically antagonizes COX-2. . . . 15-PGDH transcript and protein are both highly expressed by normal colonic epithelia but are nearly undetectable in colon cancers.” These authors employed gene transfection for restoring 15-PGDH expression in CRC cells, which strongly inhibited their ability to form tumors in immune-deficient mice, thereby demonstrating that 15-PGDH was capable of functional CRC tumor suppressor activity. They concluded that “colonic 15-PGDH expression is directly controlled and strongly induced by activation of the [tumor growth factor- β] TGF- β tumor suppressor pathway. [Findings of which] delineate an enzymatic pathway that induces colon cancer suppression, a pathway that is activated by TGF- β and mediated by 15-PGDH.” The next logical step will be to apply this knowledge to humans, and such hereditary CRC-prone disorders as FAP and the Lynch syndrome will be excellent targets for this research.

In the next decade, molecular and genetic approaches will likely take center stage in the prevention, diagnosis, and treatment of cancer. It will be essential that physicians remain well informed so that they may successfully harness the power of these approaches to the benefit of patients.

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9. The mentor should provide the fellow with a sufficiently discrete area of study, one that is identifiable to the fellow and that does not have significant overlap with other fellows working with the mentor. The general theme of research might be similar among fellows, but the areas of study should be different, otherwise career development might become difficult as disputes develop about ownership of preliminary data for future projects or grant applications.
10. There should be a history of successful transitions from fellow to staff or independent investigator by former fellows who have rotated through the prospective mentor's laboratory.

Additional Remarks

How much time should a fellow expect to spend with a mentor?

The amount of time a fellow spends with his or her mentor will vary from day to day and week to week. In my program, I assure fellows that I will meet with them every

day. This meeting may be as brief as a greeting in the hallway or a cup of coffee together, or as extensive as a few hours of work together on a manuscript or a day spent with a designated statistician analyzing data. Regardless of the specific amount of time, it is recommended that there be some interaction between the fellow and the mentor every day that they are together in the workplace. This interaction affords the fellow opportunities to ask questions or raise issues. I also maintain an "open door" policy: my office door is never closed, and fellows know that they can inquire any time that I am there about when I have time to meet. It may not be possible for all mentors to be available on a daily basis, but this is the ideal situation.

What is an appropriate number of fellows per mentor?

This number depends on the resources available. How much time does the mentor have for fellows? Does he or she have a K-24 award from the NIH? It is difficult to generalize, since each mentor's situation is different. However, more than 3 fellows per mentor is typically too difficult to manage while providing a fruitful and mutually beneficial experience.

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